REMARKS

1. Status of the Claims

Claim 1 has been amended to recite a stabilizing formulation wherein the concentration of the non-ionic detergent is between 20 ppm and 50 ppm, and wherein said formulation "does not contain polyethylene glycol (PEG)". Support for these amendments can be found in the Specification of the present application as filed, in particular in original claim 6, as well as at page 2, lines 14 to 20 and at page 2, lines 26 to 31.

Claim 2 has been amended to be in independent form including all of the limitations of claim 1 and to recite that the claimed stabilizing formulation consists "essentially of" a sugar alcohol, glycine and a non-ionic detergent.

Claim 3 has been amended to depend solely on claim 1.

Claim 1-11 have been amended for improved grammar.

Claim 6 has been canceled.

Claim 11 has been amended to correct a typographical error.

Claims 15 to 17 have been added. Support for these claims can be found in original claims 3 to 5.

2. Rejection under 35 U.S.C. § 102(b) over U.S. Patent 6,267,958

Claims 1, 3, 4 and 6-11 have been rejected by the Examiner as being anticipated by US 6,267,958, as is evidenced by the MDMS for mannitol. This rejection is respectfully traversed.

The Examiner urges that US 6,267,958 describes an Ig formulation comprising mannitol (the concentration of which) is 250 mM (i.e. 45.5 g/l), glycine and and non-ionic detergent (polysorbate, the concentration of which is 0.005% (i.e. 50 ppm)), and urges that these teachings anticipate the formulation claimed in the present invention.

Applicants respectfully disagree for the following reasons.

As disclosed from column 1, line 62 to column 2, line 3, US 6,267,958 describes a

> "*stable lyophilized protein formulation which can be prepared using a lypoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilised formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (...) than the protein concentration in the pre-lyophilized formulation.*"

Among the various formulations disclosed in the examples, Applicants submit that formulations comprising mannitol, glycin and Tween 20 are disclosed in example 1 only:

- at table 2, column 20, line 11, a formulation is described, which comprises 21 mg/ml of protein, 250 mM mannitol, 25 mM glycin and 0.01% Tween 20, in a buffer comprising 10 mM sodiul succinate at pH 5.0;
- at table 2, column 21, line 1, a formulation is described, which comprises 21 mg/ml of protein, 54.9 mM mannitol, 266.4 mM glycin, and 0.01% Tween 20 in a buffer comprising 10 mM histidine at pH 6.0.

As explicitly indicated in this example, the concentration of the non-ionic detergent in the disclosed formulations is 0.01%, which corresponds to 100 ppm. It therefore appears that these formulations fail to anticipate the formulation claimed in amended claim 1, wherein the non-ionic detergent is comprised in a concentration of between 20 and 50 ppm.

In the Office Action, the Examiner further considers that table 9 of the '958 patent discloses compositions wherein the concentration of polysorbate is 0.005% (i.e. 50 ppm). Applicants respectfully disagree and specifically points out that table 9 unambiguously refers to

compositions containing either sucrose or trehalose in an isotonic or hypotonic concentration, in a buffer containing histidine and polysorbate. Table 9 nevertheless fails to disclose any composition comprising glycine, a sugar alcohol, such as mannitol, and a non-ionic detergent. See in particular column 30, lines 54 to 59:

> "*Table 9 below shows the number of particles of size equal to or greater than 10 tm and equal to or greater than 25 μm from the isotonic and hypertonic sucrose and trehalose formulations. Polysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01% and 0.02% prior to lyophilization.*"

Further, examples 1 or 2 of the '958 patentcontain no suggestion or indication that sucrose and/or trehalose disclosed in the formulations of table 9 might actually be replaced by both glycine and a sugar alcohol such as mannitol, nor do they contain any indication that the formulations disclosed in table 2 might actually be modified such as to reduce the concentration of polysorbate.

On the contrary, US 6,267,958 explicitly indicates that the combination of mannitol and/or sorbitol with glycine is detrimental (and should therefore be avoided) for preparing stabilizing compositions for immunoglobulins, since this combination is purported to result in the aggregation of the proteins during storage. See in particular column 20, lines 11 to 16:

> "*The formulations at 5.0 mg/ml protein containing either sorbitol or mannitol yielded aggregated protein after storage at 40°C for 2 weeks. At the higher protein concentration (21.0 mg/ml), formulations comprising mannitol, or mannitol in combination with sorbitol or glycine, contained aggregated protein after lyophilization and storage at both conditions. In contrast, trehalose and sucrose prevented aggregation at both storage conditions*",

and column 20, lines 33 to 39:

> "*The addition of sucrose at an equal mass to mannitol (10 mg/ml of each) in the histidine formulation stabilized the protein against aggregation for both storage conditions. <u>The use of glycine with mannitol did not improve the protein stability</u>, while the sucrose/glycine formulation provided the same stability as the sucrose/mannitol formulation. These results further indicated that sucrose was useful for preventing aggregation of the lyophilized protein during storage.*"

Applicants further submit that this point was explicitly discussed and addressed in the Specification of the present application, in particular at page 3, lines 1 to 9, which discloses that:

> "*The international patent application WO 97/04801* (N.B. corresponding to US 6,267,958) *discloses the effect of stabilisation of lyophilised monoclonal antibodies formulations (immunoglobulins of G and E type) comprising specific excipients. From these excipients, the combination of glycine/mannitol was not selected because of lack of efficiency compared with other combinations, such as sucrose/glycine and sucrose/mannitol.*"

Applicants therefore submit that US 6,267,958 fails to disclose the stabilizing formulation claimed in amended claim 1, since the reference can only be considered as anticipatory when it contains all of the claimed features. Withdrawal of the corresponding rejection is, therefore, respectfully requested.

3. Rejection under 35 U.S.C. § 102(b) Over U.S. Patent 5,945,098

Claims 1, 3, 5-7, 9 and 11 have been rejected as being anticipated by US 5,945,098, as evidenced by the MDMS for glycine. This rejection is respectfully traversed.

The Examiner urges that US 5,945,098 teaches an aqueous IgG formulation comprising mannitol, glycine in a concentration of from about 0.1M to 0.3M (i.e. 7g/l to 21 g/l) and polysorbate 80, in a concentration of from 0.002% to 0.004% (i.e. 20 ppm to 40 ppm), and considers that these teachings anticipate the formulation claimed in the present invention.

Applicants respectfully disagree for the following reasons

As disclosed in its abstract, lines 1-4, US 5,945,098 describes:

> "*Stable, intravenously-administrable immune globulin preparations* (which) *are stabilized against aggregation and polymerization and rendered isotonic with amino acid(s) and non-ionic detergents, polysorbate and polyethylene glycol.*"

Applicants respectfully submit that all the stabilized formulations disclosed in US 5,945,098 actually contain polyethylene glycol, which is purported to be important for ensuring the overall stability of the immunoglobulins compositions. See in particular column 6, lines 4 to 11, as well as examples I to V, which are all directed to aqueous IgG solutions containing polyethylene glycol:

> "*While PEG alone cannot provide a preparation as stable as those described herein, its presence is believe to be important to the overall stability of any immune globulin solution, including those of the present invention. Thus, if PEG is not already present in the starting source of immune globulin, a small amount (typically less than 0.2 gram %) should be included in the preparations of the invention.*"

Applicants therefore consider that US 5,945,098 fails to disclose any stabilizing formulation which does not contain PEG, such as those claimed in the present application.

In view of the above mentioned elements, Applicants thus consider that the subject matter of amended claim 1, and thus of claims 3, 5-7, 9 and 11 is novel with respect to the disclosure of US 5,945,098. Withdrawal of the corresponding rejection is thus respectfully requested.

4. Rejection under 35 U.S.C. § 103(a)

Claims 1, 8, 10 and 11 have been rejected as being unpatentable over US 5,945,098 in view of US 6,267,958. This rejection is respectfully traversed.

The Examiner urges that US 5,945,098 differs from the present invention only in that it does not teach the lyophilized composition of claim 8, and that a skilled person in the art, at the time the invention was made, would have been motivated to employ the lyophilisation method as taught by US 6,267,958 to the antibody formulation as taught by US 5,945,098.

Applicants respectfully disagree for the following reasons.

As discussed previously, US 5,945,098 fails to disclose any stabilising formulation which does not contain PEG. Applicants submit that, as indicated in the specification of the present application, the stabilizing formulations provided by US 5,945,098 are not suitable for lyophilisation since PEG induces the precipitation of immunoglobulins upon lyophilisation. See the present application, in particular at page 2, lines 14-20:

> "*Some of these stabilisers, however, are known to be precipitating agents of proteins higher than about 100 kDa. Thus, the use of polyethylene glycol (PEG) 3000-6000 is redhibitory in the freezing phase leading to the lyophilisation of the corresponding protein compositions.*",

and at page 2, lines 26-31:

> "*Moreover, Guo et al., (Biomacromol., 2002, 3(4), p. 846-849) pointed out that the lyophilisation of horseradish peroxidase in the presence of PEG does not allow to maintain its native structure. Thus, it appears that the presence of PEG is undesirable.*"

Applicants therefore submit that the one of ordinary skilled in the art would have had no reasonable expectation of success to prepare a stabilizing formulation which is suitable for the stabilisation of immunoglobulins G compositions in lyophilised form by combining the compositions disclosed in US 5,945,098 with the lyophilisation taught by US 6,267,958.

Further, Applicants respectfully submit that since, as discussed above, US 6,267,958 explicitly indicates that the combination of mannitol and/or sorbitol with glycine is detrimental (and should therefore be avoided) for preparing stabilizing compositions for immunoglobulins, and since this combination is purported to result in the aggregation of the proteins during storage, the reference unambiguously teaches away from the stabilizing formulation of the present invention. A person of ordinary skill in the art would have had no incentive or reasonable expectation of success to prepare a stabilizing formulation comprising a sugar alcohol, glycine and a non-ionic detergent in the prescribed amount and which does not contain PEG. As disclosed in the present application, the properties of the stabilising formulation of the present invention result from the surprising synergistic effect of these three main components. See the present application discloses, in particular at page 6, lines 35-37:

> "*The addition of a non-ionic detergent has surprisingly improved, by synergy, the protecting effect of the formulation.*"

In view of the above, Applicants submit that the Examiner has failed to demonstrate a case of prima facie obviousness of the present invention over US 5,945,098 in view of US 6,267,958. Withdrawal of the corresponding rejection is therefore respectfully requested.

In view of the above amendments and remarks, Applicants believe that the pending application is in condition for allowance.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $130.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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